REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the remarks which follow.

Applicants have amended claim 26 to insert formula (V) which inadvertently was omitted from the prior Amendment.

In addition, claims 44-46 have been cancelled without prejudice or disclaimer and new claims 47, 48 and 49 have been added. These new claims are fully supported in the as-filed specification.

Claims 26-46 stand rejected under 35 USC § 103(a) as being unpatentable over the combination of Jones et al. U.S. 4,358,593 in view of Jones et al. EP 62503 and in further view of Alt, U.S. 5,523,416. This rejection is respectfully traversed.

The claimed invention recites a process for preparing raloxifene hydrochloride in a pure and crystalline form, the process being simplified compared to those known from the prior art. While it may be true that the process depicted in claim 26 (and claims depending thereon) is similar in its initial part to the known processes, particularly to the process described in Jones, US pat. 4,358,593 (Jones '593), it differs from the known processes in its last steps d1) and d2). As is demonstrated hereinbelow, these two steps, besides being simple ones which result in a greatly simplified process, also afford better yields of the final product.

The improved yield feature of the present invention, which so far has been disregarded by the Examiner, is on the contrary extremely important, as is well-known to any pharmaceutical manufacturer and it deserves a short presentation before addressing the actual arguments of the Examiner.

With the process of the claimed invention, assuming the intermediate (IV) as the basis for the evaluation of reaction yield, a yield of 70.4% of the desired product is obtained (see the end of example 2 of the application). The only document of the cited

prior art in which it is possible to quantitatively evaluate the yield is US Patent, 4,358,593. There, in example 9 it is said that 20 g (equivalent to 0.061 moles) of 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]itthiophene (namely, intermediate (IV) of the present invention) is reacted with 26.3 g of 4-(2-piperidinoethoxy)benzoyl chloride, hydrochloride (equivalent to 0.092 moles). The preparation of raloxifene is completed in example 26 of US Patent, 4,358,593, in which it is stated "*The oily product of example 9, above, was dissolved ....*", then the hydrolysis process is described, and the end is "*... to obtain 11.9 g of product, ...*", where by product is meant raloxifene. As raloxifene has a molecular weight of 473.58, it means that 0.025 mol of product are obtained. This leads to a yield over intermediate (IV) of 0.025/0.061 ≈ 41%.

The yield of 70.4% of the present invention thus represents a 71.9% improvement over the known process. In the field of organic chemistry, and in particular of pharmaceutical chemistry, a 71.9% improvement in yield is surely an indication that the two compared processes cannot be considered similar, and that the differences between the two cannot be considered merely "*modifications by analogy*" leading to similar results, as would be required for a determination of obviousness.

Turning now to the Examiner's rejections, an examination of the differences between the process of the claimed invention and the closest one derivable from the cited prior art are in order. Examining the processes in detail, the synthesis route of the claimed invention is similar to that of Jones '593 up until the hydrolysis of the compound 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene. At this stage, however, the two syntheses diverge as shown in the table below (the relevant part of the synthesis is described in Jones '593 in example 26), in which Applicants have tried to place side-by-side comparable process operations:

Comparative Table

Example 26 of Jones '593:	Last part of claim 26 of the present application:
The oily product of Example 9 above, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-	d1) treating 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-

piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride, was dissolved in 700 ml of methanol and 100 ml of 5 N sodium hydroxide.	piperidinoethoxy)benzoyl]-benzo[b]thiophene with a 30% water solution of sodium hydroxide in methanol solvent, using an amount of sodium hydroxide solution such that the hydroxide is in stoichiometric excess
The mixture was ... evaporated to an oil under vacuum at a temperature below 40 °C.	
The residue was dissolved in 500 ml of water and washed twice with 500 ml portions of diethyl ether.	d2) adding to the reaction mixture obtained in stage d1) equal weight quantities of water and ethyl acetate,
The aqueous layer was acidified to pH 2 with cold 50% aqueous methanesulfonic acid,	followed by acidifying said reaction mixture with 37% concentrated hydrochloric acid, to obtain the corresponding raloxifene salt with the strong acid
diluted to about 3 liters, and washed twice with 1 liter portions of diethyl ether.	washing the suspension obtained in stage (d2) with equal weight quantities of water and ethyl acetate.
The aqueous layer was then separated, thoroughly degassed under vacuum, and made basic with aqueous ammonia.	
The resulting solids were collected by filtration and vacuum dried at 40 °C to obtain 14.2 g of crude product which was chromatographed over a 5×5 cm column of Activity I silica gel, eluting with 15% methanol in chloroform.	
The product-containing fractions were evaporated to dryness to obtain a yellow foam,	
which was recrystallized from acetone to obtain 11.9 g of product.	
Here is needed a further step of salification with hydrochloric acid, not described in example 26 of Jones 4,358,593, to obtain the raloxifene salt obtained by the present invention	

The Examiner rejects claims 26-46 as obvious over Jones '593 in view of EP 62503 and further in view of Alt, US Patent 5,523,416 (Alt '416). According to the

Examiner (Section "*Scope & content of prior art*", pages 3 and 4 of the Office Action), Jones '593 discloses a process that is very similar to that of the present invention. In the section "*Differences between prior art and the claims*", at the middle of page 4 of the Office Action and onward, the Examiner asserts that Jones '593 differs from the present claims for the fact of not disclosing direct production of raloxifene hydrochloride in the last steps of the preparation route by use of concentrated hydrochloric acid, and for the fact of not disclosing the production of the starting di-hydroxy compound by demethylation of the corresponding di-methoxy compounds. However, according to the Examiner, the first teaching (of using concentrated hydrochloric acid at the end of the process) is provided by Jones '593 itself, at col. 8, lines 8-30, while the teaching about deprotection of the di-methoxy compound is complemented by either EP 62503 or Alt '416.

Applicants most respectfully disagree with this characterization of the claimed invention, of the prior art, and of the differences between the two.

In the first place, in the first half of page 4 of the Office Action, the Examiner asserts that Jones '593, at example 9, describes "*... 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(piperidinoethoxy)benzoyl]-benzo[b]thiophene hydrochloride a small portion of which is recrystallized from ethanol ....*", and "*... 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(piperidinoethoxy)benzoyl]-benzo[b]thiophene was then deprotected by treatment of sodium hydroxide in methanol, followed by acidification to pH 2-3, then readjusted to pH 8 which resulted in ... raloxifene*". ***The above is simply not correct.*** It is submitted that nowhere in example 9 of Jones '593 is there described the step of recrystallization from ethanol. Insofar as the treatment with sodium hydroxide followed by hydrochloric acid is concerned, a similar (not the same) treatment, at most, is described in example 26, but this example does not disclose acidification to pH 2-3, followed by readjustment at pH 8.

Accordingly, Applicants do not understand exactly on what the Examiner's reasoning is based. Seemingly, in the Examiner's estimation what is to be considered is the starting point in Jones '593, which when complemented with other disclosures in the same or other prior art documents, would lead to the claimed invention. Examples 14-25

and 2-33 of Jones '593 are about the preparation of compounds of the same family of raloxifene, but different from raloxifene, or the preparation of raloxifene through different process intermediates. In all of these examples, when it comes to isolating the final product (raloxifene or a similar product), a lengthy sequence of steps is consistently adopted comprising evaporation under vacuum, different washings, and chromatography purification similar to the one described in the table above (there may be differences in specific cases).

Accordingly, it is respectfully submitted that by reading the prior art documents in combination, one of ordinary skill in the art would never have thought of eliminating the vacuum evaporation step, which is consistently used in the cited prior art, thus leading one of ordinary skill in the art to believe that that is a necessary step. Similarly, no motivation, suggestion or hint can be found in the cited prior art to replace the sequence of steps shown in the last part of the table above, comprising a chromatography purification, in favor of the much simpler step of the addition of concentrated HCl, and washing with the particular mix of solvents of the claimed invention.

The teachings of EP 62503 or Alt '416 do not ameliorate or overcome this deficiency. These two references, which are assigned to Eli Lilly, and thus likely from the same research group or division, describe processes similar to those in Jones '593, with the same drawbacks, namely, a description of a much more complex and burdensome process in its last steps than the last steps of the claimed invention.

The teachings of EP 62503 or Alt '416 according to the Examiner serve to complement the information about the production of a di-hydroxy compound starting from a di-methoxy compound (starting compound of the synthesis of the present application). In fact, they are both totally useless in supporting the Examiner's arguments, inasmuch as the difference between the process of the claimed invention and what distinguishes it from the prior art and imparts unobviousness to the claimed invention, resides in the last steps of these processes (a point which the Examiner seems not to have appreciated).

Thus, the "*Prima facie obviousness*" finding set forth between pages 5 and 6 of the Office Action is totally groundless. The first part of this paragraph deals with the demethylation of a di-methoxy compound to give a di-hydroxy compound, but as stated above, this part has to do with the first step of the complete process, while the inventive part of the present invention, and that which is clearly unobvious to one of ordinary skill in the art, resides in the last steps.

Soon thereafter, the Examiner also contends that "*The adjustment of particular conventional working conditions ... is deemed merely a matter of ... selection and routine optimization ...*" However, in the decision *In re Mostovich* which he cites, it is required that information necessary for arriving at the invention be "beneficially taught" by the prior art, in order to find that the invention is obvious. **In the present situation, there was no teaching whatever in the prior art as to steps d1) and d2) that are critical to the claimed invention and that result in the obtention of a dramatically improved and totally unexpected yield (see below) by means of a simplified process**. Thus, it is Applicants' position that the cited prior art does not "beneficially teach" the limitations of the invention as presently claimed.

The number of possible modifications of a chemical process, be they in terms of reactants, solvents, temperature, catalysts, ..., is essentially infinite, so absent such a "beneficial teaching" the skilled artisan, with knowledge of a given process and seeking to improve it, has no idea where to look or what steps to take to reach his goal. In the present instance, nowhere in the references is it said or inferred that it is possible to avoid the vacuum evaporation step, which results in obtaining an oil, and the consequent burdensome sequence of steps depicted in the second part of the table produced above, to yield the product of interest, namely, crystalline raloxifene hydrochloride.

Thus, the "routine optimization" of *In re Mostovich*, absent a hint of the right direction in the prior art in which to head, is essentially a task that could require years of trials. Reminding the Examiner again that it is likely that the three (3) cited prior art documents all originate from the same research group or division, if the present invention was, indeed, so obvious, at least at the time of filing of the Alt '416, the most recent piece

of art, one can only wonder why the researchers at Eli Lilly, who are truly experts in these syntheses (at a level of expertise surely higher than "one of ordinary skill in the art"), did not arrive at it. The truth is that the present invention, with its peculiar limitations d1) and d2) leads to surprising and totally unexpected results even for a research group that had worked for nearly fifteen (15) years with raloxifene and its preparations.

At page 6, the Examiner adds a "*New rejection*". As a preliminary aside, we note that it's not clear why the Examiner bothers with citing another reference of Alt, US Patent, 5,512,684 (Alt '684), when this stems from a continuation of the application that led to Alt '416 and thus shares exactly the same description as its parent.

Without entering into the details in depth, Applicants note that Alt '684, of course, does not add any new information to that already contained in the other three (3) documents. While the synthesis at example 5, at column 15, is closer to that of the claimed invention, it still requires evaporation under vacuum with the obtainment of an oil that is not further purified (lines 52-53). Alt '684 does not say any more about how, from this oil, one can arrive at the final product in a useful form (purified and crystalline) Thus, the skilled artisan, starting from Alt '684 and looking for the missing information, could only refer to one or more of Jones '593, EP 62503 or Alt '416. As discussed at length previously, in none of these documents would the skilled artisan have found any useful information as to how to avoid the burdensome last steps of the processes described in the documents assigned to Eli Lilly, and much less would he have found any hint or suggestion towards the specific steps d1) and d2) of the claimed invention.

According to the Examiner (see the discussion between pages 6 and 8 of the Office Action), Alt '684 is compared to the claimed process. It is said by the Examiner to only differ because Alt isolates the crude product and does not cite the purity of the final product. The first statement suffers from the same pitfalls already identified above since Alt '684 contains exactly the same examples as Alt '416.

By reading Alt '684 the skilled artisan would have understood that it is necessary to employ a long sequence of steps, at the end of the complete synthesis process, to

isolate the desired product. Nowhere in Alt '684 (or in any other of the cited documents) would the skilled artisan have found a suggestion of how to avoid the complicated sequence of steps set forth in the left-hand column of the Comparative Table reported at pages 8 and 9 of this Amendment.

The section of Alt '684 identified by the Examiner (at the beginning of page 8 of the Office Action) and, in particular, the part at column 11, lines 28-39, is no more than a general indication that certain protective groups can be removed with bases or acids. However, the combination of these parts of the specification when taken with the detailed description of the process given in the examples, would never have taught the skilled artisan to skip the complex sequence of Jones set forth in the Comparative Table. In other words, col. 11, lines 1-5 or 28-39 of Alt '684, teaches at most, how to carry out the deprotection steps of the process set forth in the left-hand column of the Comparative Table at pages 8 and 9 herein, but does not teach that by operating such steps he could have avoided most of the passages therein.

The fact that Alt '684 does not describe the impurities content of his final product is presented by the Examiner as being of secondary importance, ***while it is, in fact, crucial***. The value of the presently claimed invention resides exactly in the fact that it allows the obtention of a highly pure product quite simply, so this deficiency in Alt '684 (which hides the fact that the process in Alt leads to an impure product that requires a long purification procedure) is, instead, of the ***utmost importance***.

Once again, the Examiner advances a "*Prima facie Obviousness*" case that is not supported by the evidence presented, which is similar to the situation discussed previously. Again, we have the situation where the Examiner uses the *In re Mostovich* line of argument discussed above, but again he fails to prove where in the prior art there were teachings of the pieces of information necessary to arrive at the claimed invention and, of course, there is not even an indication made by the Examiner as to where in the cited documents there is even a hint which would lead one of ordinary skill to the combination that makes the claimed invention.

Finally, at the end of the Office Action the Examiner sets forth the conclusions of the Supreme Court in the KSR decision. KSR is said to require that "... *there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.*" Applicants maintain that the Examiner has not met his burden, namely, the requirement of providing articulated reasoning showing how the combination of the three (3) prior art documents could have taught the present invention. The Examiner simply refers to "Exemplary rationales" (A) to (E) at the end of the Office Action, asserting these are supported by his previous discussion.

As previously stated, Applicants do not believe the Examiner has fully met and discharged his obligation, and he leaves it to the Applicants to complete the argument against the claimed invention with the guidance of rationales (A) to (E), ***which are not correct.*** Following the indication by the Examiner that his grounds of rejection are based on rationales (A) to (E), it can be seen that:

- Rationales (A), (B) and (D) require that the prior art teaching could have been combined, before the invention was made, to yield predictable results. It is respectfully submitted that an improvement of product yield of close to 72%, when compared to the prior art process, cannot be considered a predictable result. ***It is, rather, entirely unpredictable!***

- Rationale (C) is difficult to interpret in the present situation. While one can only guess what are similar methods (but then when can it be said in chemistry that methods are similar, and when do they cease to be similar?) It is absolutely not clear what is meant by the phrase "in the same way". In the present situation an arrangement of solvents (an equal weight water:ethyl acetate mixture) is not taught by the prior art and is not taught by the prior art for use in a sequence of steps. The differences may seem small, but the difference in results is dramatic. So, once again, when in chemistry can it be said, beforehand, that two systems are similar?

- Rationale (E), when applied to the present situation, is, to put it simply, misguided. To find that something was "obvious to try" it is required that the possible alternatives to be tried are limited in number. Faced with the teachings of the prior art,

where there were several process steps, each of which could be carried out in an essentially infinite number of conditions of temperature, reactants, solvents and blends of different solvents, one of ordinary skill in the art would have had absolutely no guidance whatever from the prior art as to the choice of the particular sequence of steps d1) and d2) of the claimed invention, and of the specific use of an equal weight mixture of water and ethyl acetate.

Summarizing the discussion above, it can be said that:

- the Examiner has still failed to properly demonstrate, with "articulated reasoning," as required by the KSR decision, which was cited by the Examiner, why it would have been obvious, at the time the invention was made, to modify some features of the processes of the prior art (or to add or eliminate some of them) to arrive at the presently claimed invention;

- the prior art taught a process for the preparation of raloxifene whose last steps were rather complex and burdensome, which led to mediocre yields. Moreover, one of the treatments common to all the cited prior art documents is chromatographic purification after acidification. That, quite obviously, is not applicable to an industrial process, which makes the prior art process essentially only a theoretical demonstration of the complete synthesis. By contrast, the process of the claimed invention, characterized by the limitations d1) and d2), affords a much higher yield in a simpler and more straightforward way. ***Simply put, the claimed invention provides an elegant and unexpected solution which is entirely unexpected and unobvious in view of the art.***

Given these failures and differences, it is the Applicants' view that the Examiner's opinion of obviousness is necessarily based on the perfect hindsight of Applicants' own disclosure. If modifications of a previously known process reside in simple steps, it is always easy, afterwards, to think that these could have been thought of rather easily and simply. However, it is clear that the Examiner fails to make a distinction between a modification consisting of simple steps, and the simplicity of predicting beforehand what advantages and results these modifications could have brought about. The fact that the deviations from the prior art are simple is not the

standard for a finding of obviousness. Rather, it is exactly the contrary that's true, ***a simplification of the prior art leading to advantages is clear evidence of inventiveness and unobviousness.***

In view of the above, Applicants believe that the claims which are currently pending serve to distinguish over the art. Since the § 103(a) rejection has been overcome, its withdrawal is solicited since Applicants have clearly demonstrated by a preponderance of the evidence that the Examiner has failed to prove that the claimed invention is *prima facie* obvious.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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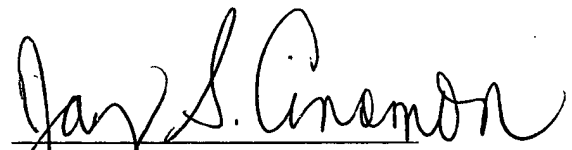
By 
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